## REMARKS

Claims 1-5, 7-11, and 16-20 are pending in the present application.

The rejections of: (a) Claims 1-5 and 7 under 35 U.S.C. §103(a) over Nakajima et al in view of Georges et al[1], and (b) Claims 1-5 and 7 under 35 U.S.C. §103(a) over Nakajima et al in view of Georges et al and Ueda et al, are respectfully traversed.

The Examiner has taken the position that the claims are obvious over Nakajima et al (Exp. Cell Res. 1998) in view of Georges et al, with or without Ueda et al (J. of Antibotics, 1994). It is the Examiner's position that Nakajima et al discloses a compound of formula (I) and (II) (i.e., FK228) is an inhibitor of intracellular histone deacetylase activity that strongly inhibits proliferation of tumor cells *in vitro* and greatly suppresses the growth of transplanted tumors in mice (citing page 126). However, the Examiner recognizes that Nakajima et al fail to specifically disclose the treatment of kidney cancer or suppression of a cancerous tumor in the kidney.

Ueda et al disclose that FR901228 shows the suppression of the proliferation of tumor cells not only *in vitro* but also in SRC assay using A549 lung adenocarcinoma or MCF-7 mammary adenocarcinoma, as shown in Table III on page 308.

With regard to Georges et al, the Examiner states, "Georges et al. teaches a method of treating the proliferation of malignant cell and cancer of the breast, ... as well as solid tumors of kidney, ... , with a histone deacetylase inhibitor". With respect to the allegations related to Georges et al in particular, Applicants disagree with the Examiner's allegations.

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1 Not immediately clear from the Office Action, but appears to be still a ground of rejection and, as such, is included in the traversal.

Notably, Georges et al discloses that an unrelated collection of compounds have been found to possess anti-cell-proliferation properties arising from their histone deacetylase inhibitory activity (see paragraph [0036]). Georges et al then concludes that due to the anti-cell-proliferation properties, their compounds "are expected to be useful in the treatment of cancer... particularly in the treatment of cancers of the breast, lung, colon, rectum, stomach, prostate, bladder, pancreas, and ovary." Georges et al further speculate that "It is in addition expected that a derivative of the present invention will possess activity against a range of leukemias, lymphoid malignancies and solid tumors such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas" (see paragraph [0036]). Accordingly, it must be noted that Georges et al provides nothing more than mere speculation of an unsupported "expectation" that their compounds would work for treating virtually any form of cancer. Certainly, this does not provide any reasonable expectation that the compounds of the presently claimed invention would successful for treating kidney cancer.

Georges et al disclose HDAC inhibitory activity (Example 12) of the compound of the formula I, but does not disclose or suggest suppression of proliferation of malignant cell in any cancer, nor does it show any pharmacological data supportive of such effect.

Indeed, at no point do Georges et al disclose or suggest that HDAC inhibitor suppresses kidney cancer nor do Georges et al provide any reference citation that discloses the same. In the "Background Of The Invention" (on last 6 lines of paragraph 1 on page 1), Georges et al disclose that an HDAC inhibitor has already been found to suppress proliferation of colon cancer, T-cell lymphoma and erythroleukemic cells.

As a review of the HDAC inhibitor, Georges et al cites Marks et al, J. Natl. Cancer Inst. 92 (15), 1210-1216, (2000) (copy **submitted herewith**) (paragraph 2 on page 1). The Marks

et al reference reports *in vivo* pharmacological test results including clinical tests of various HDAC inhibitors (see, the second paragraph, "In Vivo studies With HDAC Inhibitor" on page 1214). According to Marks et al, pharmacological tests using animal models were performed for plural HDAC inhibitors, and suppression of the proliferation of tumors such as breast, prostate, lung and the like was observed. However, no report refers to kidney cancer and the potential efficacy of any HDAC inhibitor. In the second paragraph, two other HDAC inhibitors are mentioned, which again fail to describe HDAC inhibitor activity against kidney cancer.

The Examiner's general position with respect to the disclosure of Georges et al on page 3, paragraph 36, lines 10-19, is based on the expectation that, given the HDAC inhibitory activity confirmed in the compound of the formula I, combined with the finding relating to known HDAC inhibitors, the compound of the formula I must similarly have an anti-proliferative effect. However, as described above, the type of cancer recited in the cited references includes, in addition to those cancers for which other known HDAC inhibitors have already been confirmed to be effective, kidney cancer on which no report was found at the time of filing of the application. Kidney cancer is not at all the type of cancer for which an effect is "expected" from the findings of known HDAC inhibitors. Inasmuch as Georges et al do not disclose a basis for the expectation of an effect for kidney cancer, no such conclusion can be reasonably drawn from Georges et al. Therefore, Applicants submit that the Examiner's allegation that Georges et al disclose an effect for treating kidney cancer is incorrect.

Applicants further submit that the skilled artisan would appreciate that sensitivity to anti-tumor agents varies depending on the type of cancer, and the type of cancer that proves effective should be ascertained by panel tests and the like. Likewise, the sensitivity to HDAC inhibitors, including toxicity, has also been studied. For example, as shown in Nishimura et al.,

page 556, Table 4, submitted on April 30, 2008, those having ordinary skill in the art usually perform *in vivo* cancer proliferation suppression tests (sensitivity tests) with regard to the target cancer, so as to know what site or which type of cancer an anti-tumor agent is effective for. As shown in Table 4 of FR900840 cited in Nishimura et al., each anti-tumor agent is known to show different effects depending on the tumor site and the type of tumor cells. Hence, the effect of an HDAC inhibitor for kidney cancer cannot be predicted even when some references (Nakajima et al. and Ueda et al.) disclose that the HDAC inhibitor is effective for other types of cancer, since no other HDAC inhibitors have exhibited an effect for kidney cancer, and therefore, no motivation can be found to apply the HDAC inhibitor to kidney cancer.

Applicants again strongly argue that it is not proper to conclude, "use for the treatment of kidney cancers is enough for a skilled practitioner to obviously try" with regard to the compound of the present invention. The reasons, therefore, are that Georges et al only provide a broad disclosure with a desirous effect of the compound but without a support for the alleged effect, the present compound has a completely different structure, and that the mere presence of the same mechanism is not sufficient to reach a conclusion of efficacy.

Further, Applicants again wish to direct the Examiner's attention to page 2, lines 2-7, which provides a general view of the state of the art at the time of the present invention stating:

> As the situation stands, however, there are many problems yet to be solved, such as effectiveness of *in vitro* results in *in vivo* application, *in vivo* effectiveness against any tumor and the like. The antitumor activity *in vitro* against kidney cancer has been reported, but an antitumor activity *in vivo* against kidney cancer has not been reported.

Based on the foregoing, Applicants submit that there is no direct expectation of *in vivo* efficacy from the *in vitro* observation of HDAC inhibitory activity. This lack of expectation of success is clearly manifest in the combined disclosures of Nakajima et al and Georges et al.

Nonetheless, the Examiner again states on page 11 of the Office Action, "In regards to expectation of success for *in vivo* efficacy based on *in vivo* data, the prior art demonstrates that *in vitro* data does relate to efficacy of kidney tumors *in vivo*, as taught by Ueda et al." The Examiner's opinion seems to involve a misunderstanding, as described below.

The Examiner's apparent position is that the experiment bridging pages 303-304. However, Applicants respectfully submit that the cell lines used in this *in vivo* study are A549 and MCF-7, which are human ***lung*** adenocarcinoma and human ***mammary*** adenocarcinoma respectively. Further, the above-referenced text clearly states that these cells were transplanted ***under*** the kidney capsule of BDF1 mice. Thus, none of these experiments provide any suggestion to ***treat kidney cancer*** or any expectation of the efficacy when so doing. Therefore, Ueda et al does nothing to compensate for the deficiency in the combined disclosures of Nakajima et al and Georges et al.

The Examiner is further reminded that lung cancer cell lines, breast cancer cell lines, and kidney cancer cell lines are distinct. As such, just because a breast cancer cell is grown *on* the kidney does not instantly make it "kidney cancer." It remains a breast cancer cell that is grown on the kidney. Further, the following is found in Ueda et al on page 303, lines 6-4 from the bottom, which clarifies that the *in vivo* test uses the method of Nishimura et al called SRC assay:

> "In Vivo Antitumor Activity of FR901228
> A two-week Subrenal Capsule (SRC) assay using the immunosuppressive agent FK-506 was performed according to the method described by Nishimura et al.[17,18]"

In response, Applicants submitted with the Amendment filed April 30, 2008 the following references:

Nishimura et al, The Journal of Antibiotics Vol. XLII No. 4 (April 1989): 553-557;

Abstract of Gan to Kagaku Ryoho, 1987 May; 14 (5 Pt 2): 1629-35; and

Bogden et al, Exp Cell Biol. 1979; 47(4): 281-93.

In Nishimura et al., the Subrenal Capsule (SRC) Assay is described on page 555. In addition, Gan to Kagaku Ryoho, 1987 May; 14 (5 Pt 2): 1629-35 and Exp Cell Biol. 1979; 47(4): 281-93 discuss the SRC Assay. These references teach that the SRC Assay is a sensitivity test (chemosensitivity test) of anticancer drugs and, by comparison with a subcutaneous transplantation assay in nude mice, they state that the tumor growth inhibition rates of the SRC assay were corrected well with the clinical responses.

Therefore, it will be understood that the SRC Assay is a sensitivity test for rapid evaluation of a clinical affect of an anticancer drug for various tumors. While a tumor is implanted under the kidney capsule in the test of Ueda et al, this is clearly not for the evaluation of the effect on kidney cancer, but for the evaluation of the clinical effect of the compound on the implanted tumor itself (i.e. lung or mammary). It remains that Ueda et al do not at all suggest the efficacy for kidney tumors *in vivo*.

With respect to Bogden et al, the Examiner is referred to the Discussion on page 290, which discloses that an environment promoting the growth of xenografts (namely, human cancer cells) is present in the subrenal capsule site (first paragraph), and that the xenograft itself can be visualized due to the transparency of the renal capsule (third paragraph). It is therefore obvious that the SRC technique is a useful test method for measuring the growth of the implanted human cancer cells, utilizing the environment of the subrenal capsule site. In addition, the fourth paragraph on page 291 discloses that this method enables screening of drugs against a wider range of human tumor systems, and also enables evaluation of organ specificity as well as clinical potential. In contrast, no disclosure is found which indicates or

suggests formation of kidney cancer in the subrenal capsule by the human cancer cell implanted by this method, as alleged by the Examiner.

Further, in the Results on page 284 of Bogden et al, the growth of human cancer cells implanted under the renal capsule is disclosed in Figs. 1-6, where the results obtained by this test method concern growth of the implanted human cancer cells. Nishimura et al, The Journal of Antibiotics Vol. XLII No. 4 (April 1989): 553-557, describe in Activity against Human Xenograft Tumors on page 556 that the anticancer activity of FR900840 against 10 kinds of human cancers was evaluated by this test. Therefore, those skilled in the art understand that the SRC technique is a test method for evaluating anticancer activities of a drug against implanted human cancer cells, and even if the site of cell implantation is under the renal capsule, they obviously do not consider that the technique evaluates action on kidney cancer.

Furthermore, Nishimura et al, The Journal of Antibiotics Vol. XLII No. 4 (April 1989): 553-557 disclose on page 556, Table 4 and in lines 10 to 3 from the bottom that an *in vivo* test was performed using the FR900840 compound against 10 different tumors and the results deny activity of the compound in certain kinds of tumors. This suggests that the activity of a compound against a tumor cannot be predicted based only on an *in vivo* activity of the compound against a different kind of tumor. Therefore, contrary to the Examiner's allegation, the skilled artisan would *not* reasonably expect that the present compound would treat a tumor in the kidney in vivo based on the disclosure of Ueda et al.

It is further submitted that the presently claimed invention is drawn to an *in vivo* method. The Examiner recognizes that "Nakajima et al. and Georges et al. do not teach the Applicant's compound used *in vivo* or in a human". Thus, for the reasons given above, the

presently claimed invention is not obvious from the combined disclosures of Nakajima et al and Georges et al.

In the present invention, the claimed compound was first found to be an HDAC inhibitor effective for kidney cancer, where the usefulness of the compound was confirmed *in vivo* using animal models, as well as through clinical tests in human. Such an effect for kidney cancer was not determined with the many known HDAC inhibitors prior the present invention. Since a clinical effect was confirmed for the *first* time in the present invention, the present invention is not obvious in view of the combined disclosures of Nakajima et al, Georges et al and Ueda et al.

In view of the foregoing, Applicants request withdrawal of these grounds of rejection.

The obviousness-type double patenting rejection of Claims 1-5 and 7 over Claims 60-62, 69, and 70 of co-pending application No. 10/948,288 (now US 7,314,862) is respectfully traversed.

The claims of US 10/948,288 (now US 7,314,862) are directed to a composition comprising a compound of the formula (I) or (II) *and doxorubicin*, as well as to a method of treating cancer including kidney cancer, which comprises administering the composition, have been allowed. None of the claims of this application remotely suggest the effect on kidney cancer of the compound of formulae (1) or (2) in the absence of doxorubicin. Hence, the present subject matter directed to the method claim of treating kidney cancer of the present invention, which comprises administering the compound of the formula (I) or (II) *per se*, is not obvious from the method claim of US 7,314,862.

Withdrawal of this obviousness-type double patenting rejection is requested.

Finally, the Examiner has issued the following obviousness-type double patenting rejections:

(a) Claims 1-5 and 7 over Claims 1-3 and 9 of co-pending application No. 11/064,292; and

(c) Claims 1-5 and 7 over Claims 45 and 60 of co-pending application No. 10/486,833 in view of Georges et al.

On page 2 of the Office Action mailed November 30, 2007, the Examiner provided the following statement "The provisional obviousness-type double patenting rejections... are maintained being that terminal disclaimers have not as-yet been filed." Although it is correct, terminal disclaimers have not at-yet been filed, Applicants remind the Examiner that this is a provision ground of rejection and must be evaluated with each action with respect to the claims pending at that time to determine whether obviousness-type double patenting is actually present.

To this end, Applicants reiterate that the claims of US 11/064,292 do not specifically relate to the suppression of a cancerous tumor in the kidney. Thus, in view of this deficiency, the claimed invention is not obvious in view of US 11/064,292. Further, Claims 45 and 60 of US 10/486,833 relate to a method of treating prostate cancer, not kidney cancer. There is nothing in these claims or in Georges et al to render the present invention obvious. Thus, the present invention is not obvious.

The Examiner is also reminded that MPEP §804 indicates that: "If "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting

that application to issue without need of a terminal disclaimer." Of the three applications that are still pending (the present application, US 11/064,292, and US 10/486,833), the present application has the earliest effective filing date[2] (i.e., is the earlier filed application) and, therefore, if this application is in condition for allowance the obviousness-type double patenting rejections over US 11/064,292, and US 10/486,833 should be withdrawn.

In view of the foregoing, Applicants request withdrawal of these grounds of rejection.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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[2] The present application has an effective filing date of US 60/369,868 of April 5, 2002, while the effective filing date of US 11/064,292, and US 10/486,833 is April 29, 2004 and August 20, 2002, respectively.